REMARKS/ARGUMENTS

Applicant responds to the Examiner's comments using the paragraph numbering of the office action. Claim 11 has been amended to include the elected species from claim 13 in view of the Examiner's requirement to cancel subject matter other than elected species. Support for variants associated with hereditary amyloidosis as recited in amended claim 11 is provided by *e.g.*, at p. 18 of Table 2. Support for the recital that the immune response to an amyloid component includes antibodies is provided at *e.g.*, p. 13, lines 10-25. Support for an adjuvant that stimulates an immune response is provided at *e.g.*, p. 11, lines 10-15. Unless otherwise indicated amendments are for purposes of clarity. No amendment should be viewed as an acquiescence in any ground of rejection.

1. Traverse of the restriction requirement is maintained for the reasons previously indicated. However, the requirement is largely moot in view of the amendments to the claims. Applicant acknowledges that claim 16 has been amended to specify an alternative species (*i.e.* PrP) as well as the elected species AScr. PrP and AScr are structurally and functionally related in that PrP is a prion precursor protein that is present in normal cells and AScr is a pathogenic peptide derived from PrP, which causes prion disorders. Because of the structural and functional relatedness between PrP and AScr, it is believed that the Examiner would at most impose a species election between them. Accordingly, claim 16 is generic to the elected species and should be examined. In the event the Examiner imposes a restriction requirement between PrP and AScr, applicant reserves the right to petition the same.

5-7. Information disclosure statements.

Applicant's citation of citation nos. 144, 220, 222, 223, and 304 include all the elements required to comply with 37 C.F.R. §§ 1.97-98 that are known to them. Copies of citation nos.98, 250, and 278 are submitted herewith.

8. The specification.

The specification was objected to as having informalities. Applicant has amended the specification to correct informalities and requests that the objection be withdrawn.

The cross reference to related application section has been replaced with a replacement section which provides domestic priority information for the instant case. A supplemental ADS providing domestic priority information is submitted herewith to satisfy the specific reference requirement of 35 U.S.C. § 119(e) and § 120.

The addition of page 96, which was inadvertently omitted from the instant application as filed, to the specification does not add new matter. The instant application incorporates U.S. Application No. 60/137,010 by reference (*see* p. 2, lines 5-6 of the instant application). Support for the addition of page 96 is provided at page 87, line 29 to page 88, line 20 of U.S. Application No. 60/137,010. For the convenience of the Examiner, applicant has attached pages 87 and 89 of U.S. Application No. 60/137,010 as Exhibit A. Page 96 is attached as Exhibit B.

The specification has also been amended to conform to five of the replacement drawing sheets submitted herewith, *i.e.*, Fig. 15A, Fig. 15B, Fig. 15C, Fig. 15D, and Fig. 15E, respectively. The paragraph beginning on page 10, line 26, has been replaced with six replacement paragraphs. The replacement paragraphs describe Figures 15A-15E, 15A, 15B, 15C, 15D, and 15E, respectively. The paragraph beginning on page 94, line 1, has also been amended to identify Figures 15A-15E.

The paragraphs beginning on page 91, line 17, and page 92, line 3, have been amended to conform the alum concentration to the alum concentration recited in Figure 15 as filed in Application No. 09/201,430, filed November 30, 1998. The instant application claims priority to Application No. 09/201,430.

9. Sequence rules.

The office action mailed December 4, 2002 enclosed a notice to comply with the sequence listing rules. On May 15, 2003, applicant brought the instant application into compliance with the sequence rules by submitting the following papers to the Office, via Express

Mail Post Office to Addressee (Label No. EV 338 446 759 US), in an envelope addressed to Mail Stop Sequence, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450: a paper copy of the Sequence Listing, an electronic copy of the Sequence Listing, and an Amendment under 37 C.F.R. §§ 1.821-1.825.

10. Drawings.

Amendments to Figure 11

As requested by the Examiner, Figure 11 has been amended to add a legend. Support for this amendment can be found from page 77, line 17 to page 78, line 29 of the instant application.

Amendments to Figures 15A-15E

Figure 15D as filed in the instant application discloses an alum concentration of 2μg/ml. The replacement Figure 15D discloses an alum concentration of 2 mg/ml. Figures 15A-15E have been amended to correct an obvious error; "p Malue" has been replaced with "p Value." Support for both of these amendments is provided by the informal Figure 15 as originally filed in the parent application. Therefore, the amendments to the figures contain no new matter.

Amendments to Figure 16

As requested by the Examiner, the descriptive term "Anti AB" has been replaced with the term "Anti-Abeta" to give greater clarity to the title. Support for this amendment can be found on page 92, lines 25-33 of the instant application.

11. Claim 11 has been amended to recite the subject matter elected in previous claim 13 (which has been cancelled as redundant). The reference to mutant proteins has been amended to specify variant proteins associated with hereditary amyloidosis, and the reference to peptides or fragments of precursor proteins has been deleted as not limiting on the claim. Claims 15 and 16 have been amended to delete what the Examiner considers to be nonelected material.

12-23. Rejections under 35 U.S.C. § 112, first paragraph. Due to the length of this rejection applicant will address each paragraph in turn starting with paragraph 9.

12-13. The Examiner merely summarizes the claims. No response is required.

14. The Examiner alleges that the PDAPP mouse model does not exhibit Alzheimer's disease, Down's syndrome or other amyloidogenic disease as it occurs in humans as evidenced by Schenk, or Games. Insofar as the Examiner is suggesting that the PDAPP mouse model is not a good model of Alzheimer's disease or Down's syndrome in humans, Applicant disagrees.

The Schenk and Games references contradict rather than support the Examiner's allegations of inadequacy of the PDAPP mouse model. As noted above, Games appeared as the cover story of Nature and describes many characteristics of the PDAPP mouse that closely resemble the pathology in Alzheimer's disease. The reference concludes:

> A most notable feature of these transgenic mice is their Alzheimer-like neuropathology . . . . Our transgenic model . . . offers a means to test whether compounds that lower Aβ production and/or reduce its neurotoxicity in vitro can produce beneficial effects in an animal model prior to advancing such drugs into human clinical trials.
>
> *See* p. 527, first column, second paragraph.

Similarly, Schenk, which also formed the cover story of the edition of Nature (*see* Schenk *et al.*, *Nature*, 400:173-177 (1999)) in which it appeared, concludes:

> To our knowledge, this is the first report of a clinically relevant treatment that reduces the progression of AD-like neuropathology in a transgenic model [the PDAPP mouse] of the disease. . . . Collectively, the results suggest that amyloid-β immunization may

prove beneficial for both the treatment and prevention of Alzheimer's disease.

See p. 177 paragraph bridging cols. 1 and 2.

Thus, the Games and Schenk references support rather than contradict the view that the PDAPP mouse does exhibit many of the pathological characteristics of Alzheimer's disease, and is regarded in the art as a model reasonably predictive of results in humans.

The validity of the PDAPP mouse as a model system for predicting effects of Aβ in humans is further confirmed by the performance of human clinical trials. The Investigational New Drug Application ("INDA") supporting the clinical trials was based on essentially the same data as is contained in the present application. That the FDA allowed clinical trials to occur shows that it considered the preclinical evidence, including the results in PDAPP mouse, as being reasonably predictive of success in humans.

15. The Examiner alleges that administration of Aβ42 to Alzheimer's patients is not predictive of how administration of PrP or AScr affects patients with prion-related diseases. The Examiner alleges that there are no working examples relating to treatment of such diseases. In response, applicant attaches two publications dated after the priority date of the present invention showing that active immunization with PrP and passive administration of antibodies to PrP in a mouse model of prion disorder produces results similar to those described for immunization of Aβ (*see* Sigurdsson *et al.*, *Am. J. Pathol.*, 161, 13-17 (2002) (active); Sigurdsson *et al.*, *Neuroscience Letters*, 336, 185-187 (2003) (passive), copies attached). The authors acknowledge that their report represents an extension of previous work relating to Aβ immunization (*see Am. J. Pathol.* at p. 15, second column, first paragraph). The similarity of results for immunization with PrP and Aβ42 in mouse models of prion and Alzheimer's disease respectively indicates that administration of Aβ to Alzheimer's disease is predictive of how administration of PrP or AScr affects patients with prion-related disease.

16. The Examiner cites several papers (Lemere, Schenk, DeMattos and Raso) as evidence that therapy can be effective in removal of amyloid plaques. The Examiner does not indicate how any of this evidence detracts from enablement of the present claims. Accordingly, it is believed no response is needed.

17. The Examiner alleges one would doubt the claimed method would work due to lack of information as to specific biological actions/activities that a prion protein and an adjuvant would effect, lack of information how the immunogenic effect on amyloid deposition relates to symptoms of disease, and an alleged expectation that prion would be actively involved in amyloid deposition (citing U.S. 5,958,883). These points will be addressed in turn. The result that passive administration of prion protein achieves essentially the same results as active administration of prion protein shows that active administration of prion protein acts, at least in part, through formation of antibodies. With respect to how the immunogenic effect of prion administration relates to symptoms of disease, one would expect similar symptomatic effects results from prion administration and Aβ in view of the similarity in pathology and analogous results in mouse models described above.

Finally, the '883 patent provides no reason to think that exogenously supplied prion protein in combination with an adjuvant adds to existing amyloid deposit. The '883 patent discusses an animal model of Alzheimer's disease induced by continuous infusion of Aβ into the brain without an adjuvant. These conditions were specifically chosen to accumulate Aβ in the brain. A skilled person intending to generate an immune response comprising antibodies with a view to clearing Aβ deposits could easily avoid such a combination of conditions calculated to achieve the opposite effect. Further, applicant notes that the Examiner reliance on references discussing Aβ to infer side effects relating to prions is inconsistent with his positions that benefits from administration of Aβ cannot be extrapolated to administration of PrP or AScr.

18. The Examiner alleges that undue experimentation would be required to evaluate all possible aspects of both humoral and cellular aspects of the immune response. The Examiner cites Chapman, Frenkel (1999), Frenkel (1998), Frenkel (2000), and Freidland (1997)

as alleged evidence of the unpredictable effects of antigens on the immune system. In response, an understanding of mechanism is not required to practice the claim as presently formulated. The claims as presently formulated specify that one administers a dosage of an agent effective to produce an immune response against an amyloid component derived from a PrP in combination with an adjuvant that augments the immune response. The result of treating or preventing a prion based disease follows from performing the claims as written without the need to understand how the induced antibodies effect this result.

It is not seen that the cited references are detrimental to enablement. Freidland discusses possible use of labeled Aβ as agent for imaging plaques in the brain. However, the Aβ is not proposed to be administered with an adjuvant or otherwise to generate an immune response comprising antibodies. Thus, there is nothing in Frenkel to suggest that the combination of Aβ and an adjuvant would not be effective in preventing or treating Alzheimer's disease. The various Frenkel references investigate the role of an N-terminal epitope of Aβ, and propose to display it from a phage for use as an immunogen to generate antibodies in a mouse model of Alzheimer's disease. This proposal appears closely related to one embodiment disclosed in the present application (which predates the Frenkel references) (*see* specification at p. 11, lines 10-14). That others have incorporated the teaching of the present application into their own work supports rather than refutes enablement of the present claims. Finally, Chapman reviews three papers that test antibodies to Aβ for effects of potential treatments of both brain damage and cognitive losses caused by Alzheimer's disease. Chapman concludes that "All in all, though, these three papers give cause for optimism" (at p. 916, first column, last paragraph). Thus, again Chapman supports rather than contradicts enablement of the present claims.

19. The Examiner alleges undue experimentation would also result from inflammatory side effects (citing to Elan press releases, Grubeck Loebenstein, and U.S. 5,958,883). It is respectfully submitted that requiring a patent applicant to teach means for avoiding all side effects imposes too high a standard of enablement. Here, clinical trials have indicated that inflammatory side effects may result in a small number of patients (15 out of 360), as discussed in the Elan press releases, and Munch (of record). Moreover, in the few patients

that might experience side effects, there is the possibility of mitigation by immunsuppressants (*see* Munch at p. 1085). Few approved drugs, particularly those for treating serious diseases, are entirely free of side effects. Moreover, the requirements under the law for obtaining a patent are not as stringent as the requirements for obtaining government approval to market a particular drug for human consumption. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *Id.*

20. The Examiner alleges additional unpredictability with respect to mutants, fragments, and peptides. In response, it is noted that the recitation of mutants, fragments and peptides occurred with respect to the description of a precursor protein in claim 13. Claim 13 has been cancelled. Claim 11 does refer amyloid components derived from precursor proteins including variants thereof associated with hereditary amyloidosis. However, these are not random mutations, which may have the unpredictable effects, but rather natural mutations known to associated with amyloidogenic disease. There is no reason to think that immune responses directed to components derived from precursor proteins having such mutations would be less effective in treating prion disorders than immune responses directed to components from a wildtype precursor protein.

21. The Examiner cites Tanaka as evidence that administration of Aβ to the cerebral ventricle of rats produces learning and memory deficits accompanied by dysfunction in the cholinergic and dopaminergic systems. In response, it is noted that Tanaka administered Aβ without an adjuvant. Further, it is noted that the combination of conditions used by Tanaka was specifically chosen with a view to aggregating Aβ in the brain as a model of Alzheimer's disease rather than clearing such deposits. Thus, Tanaka administered Aβ directed to the brain, by continuous infusion, and without an adjuvant. A skilled person intending to generate an immune response comprising antibodies with a view to clearing Aβ deposits could easily avoid such a combination of conditions calculated to achieve the opposite effect.

22. The Examiner cites Smith and Weissman as suggesting that prion acquired disorders can be acquired by consumption or administration of a prior precursor protein. However, these references do not disclose administration of prion protein with an adjuvant, and as such are outside the scope of the claims as presently formulated.

23. The Examiner alleges that the application must establish a nexus between the specific immune response recited in the claims for each amyloid disorder and the alleviation of the disease state. The Examiner alleges that the skilled artisan is not guided as to how an immune response must effectuate one or more actuates of each targeted protein such that the immune response would alleviate the disorder. The Examiner also refers to variation between different amyloid disorders (citing Small, Chapman, Esiri, St. George-Hyslop, Younkin, Tennent, and Stein).

As previously discussed, the application does provide evidence that an antibody component of an immune response to peptide administration is, at least in part, responsible for alleviation of the disease state. This is shown by the result that passive immunization with antibodies achieves essentially the same results as active immunization with peptides (both with Aβ and prion protein). Further understanding of mechanisms by which antibodies lead to clearing of amyloid deposits is not required for practice of the invention. Nevertheless, the application does provide data showing that induction of a phagocytic clearing response is involved, at least in part, in the clearing response due to antibodies to Aβ (*see, e.g.*, specification at p. 116, last paragraph). The Examiner's additional comments regarding possible variation between different types of amyloid disease are moot in view of the amendment of the claims to prion-based disease.

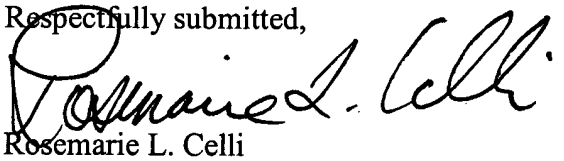
24-25. The claims are provisionally rejected for same invention double patenting over claims of several cop ending cases. Applicant requests this issue be held in abeyance until indication of otherwise allowable subject matter. It is likely in view of the restriction and election of species requirements that the claims in the cited cases will differ from those pending

in the current case at the time of allowance of the present case. However, if claims from different cases are in conflict at that time, applicant will amend the claims in the cited cases to avoid the conflict.

26-33. The claims stand provisionally rejected for obviousness type double patenting over several copending cases. Applicant proposes the issues be held in abeyance until indication of allowability in the present case. Applicant will then consider providing a terminal disclaimer over cited cases provided the cited case has been or is about to patented, the claims in the cited case have not been divided from those in the present case by restriction requirement or election of species, and the claims in the cited case are in conflict with those in the present case at this time.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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part of the toxicological evaluation, PDAPP mouse brain pathology was extensively examined as part of the efficacy endpoints. No sign of treatment related adverse effect on brain morphology was noted in any of the studies. These results indicate that AN1792 treatment is well tolerated and at least substantially free of side effects.

XI. Therapeutic Treatment with Anti-Aβ antibodies

This examples tests the capacity of various monoclonal and polyclonal antibodies to Aβ to inhibit accumulation of Aβ in the brain of heterozygotic transgenic mice.

1. Study Design

Sixty male and female, heterozygous PDAPP transgenic mice, 8.5 to 10.5 months of age were obtained from Charles River Laboratory. The mice were sorted into six groups to be treated with various antibodies directed to Aβ. Animals were distributed to match the gender, age, parentage and source of the animals within the groups as closely as possible. As shown in Table 10, the antibodies included four murine Aβ-specific monoclonal antibodies, 2H3 (directed to Aβ residues 1-12), 10D5 (directed to Aβ residues 1-16), 266 (directed to Aβ residues 13-28 and binds to monomeric but not to aggregated AN1792), 21F12 (directed to Aβ residues 33-42). A fifth group was treated with an Aβ-specific polyclonal antibody fraction (raised by immunization with aggregated AN1792). The negative control group received the diluent, PBS, alone without antibody.

The monoclonal antibodies were injected at a dose of about 10 mg/kg (assuming that the mice weighed 50 g). Injections were administered intraperitoneally every seven days on average to maintain anti-Aβ titers above 1000. Although lower titers were measured for mAb 266 since it does not bind well to the aggregated AN1792 used as the capture antigen in the assay, the same dosing schedule was maintained for this group. The group receiving monoclonal antibody 2H3 was discontinued within the first three weeks since the antibody was cleared too rapidly in vivo. Animals were bled prior to each dosing for the measurement of antibody titers. Treatment was continued over a six-month period for a total of 196 days. Animals were euthanized one week after the final dose.

Table 10

EXPERIMENTAL DESIGN OF STUDY 006

Treatment Group	N[a]	Treatment Antibody	Antibody Specificity	Antibody Isotype
1	9	none (PBS alone)	NA[b]	NA
2	10	Polyclonal	Aβ1-42	mixed
3	0	mAb[c] 2H3	Aβ1-12	IgG1
4	8	mAb 10D5	Aβ1-16	IgG1
5	6	mAb 266	Aβ13-28	IgG1
6	8	mAb 21F12	Aβ33-42	IgG2a

Footnotes

a. Number of mice in group at termination of the experiment. All groups started with 10 animals per group.
b. NA: not applicable
c. mAb: monoclonal antibody

2. Materials and Methods

a. Preparation of the Antibodies

The anti-Aβ polyclonal antibody was prepared from blood collected from two groups of animals. The first group consisted of 100 female Swiss Webster mice, 6 to 8 weeks of age. They were immunized on days 0, 15, and 29 with 100 μg of AN1792 combined with CFA/IFA. A fourth injection was given on day 36 with one-half the dose of AN1792. Animals were exsanguinated upon sacrifice at day 42, serum was prepared and the sera were pooled to create a total of 64 ml. The second group consisted of 24 female mice isogenic with the PDAPP mice but nontransgenic for the human APP gene, 6 to 9 weeks of age. They were immunized on days 0, 14, 28 and 56 with 100 μg of AN1792 combined with CFA/IFA. These animals were also exsanguinated upon sacrifice at day 63, serum was prepared and pooled for a total of 14 ml. The two lots of sera were pooled. The antibody fraction was purified using two sequential rounds of precipitation with 50% saturated ammonium sulfate. The final precipitate was dialyzed against PBS and tested for endotoxin. The level of endotoxin was less than 1 EU/mg.

The anti-Aβ monoclonal antibodies were prepared from ascities fluid. The fluid was first delipidated by the addition of concentrated sodium dextran sulfate to ice-cold

for the measurement of antibody titers. Treatment was continued over a six-month period for a total of 196 days. Animals were euthanized one week after the final dose.

Table 12

Experimental Design of Study 006

Treatment Group	N[a]	Treatment Antibody	Antibody Specificity	Antibody Isotype
1	9	none (PBS alone)	NA[b]	NA
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3	0	mAb[c] 2H3	Aβ1-12	IgG1
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